Intubation Conditions Achieved With Rapid Co-administration of Rocuronium and Propofol Versus Classical Induction: A Prospective Randomized and Blind Trial

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A Prospective Randomized and Blind Trial.

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1. Background

In the past century, measures have been increasingly implemented in the field of anesthesia to combat the incidence of preoperative and perioperative complications. However, management of a difficult airway in perioperative settings, emergency rooms, critical care units, and pre-hospital settings remains challenging. Due to this, suboptimal outcomes associated with management of patients with a difficult airway can occur, particularly if the difficulty is unexpected. A difficult airway can be due to difficult mask ventilation, difficult ventilation with supraglottic airway, and difficult tracheal intubation. The most severe scenario of difficult airway is when a "cannot intubate and cannot ventilate" scenario is encountered, the patient's oxygenation is significantly compromised, and the return of effective spontaneous breathing is not possible in a timely fashion. The recommended default rescue measure is invasive airway access(1, 2) However, a large-scale study demonstrated that the success rate of invasive airway access performed by experienced anesthesiologists is only about 35%.(3) Therefore, the search for an alternative way to save the lives of patients with difficult airways is an unmet demand and requires urgent attention and effort.

Management of a difficult airway has focused on the improvement of ventilation and intubation. Resumption of spontaneous breathing is the last option before invasive airway access is attempted. Previous reports indicate that the return of effective spontaneous breathing is unlikely in most patients if a "cannot intubate and cannot ventilate" event is encountered, due to the limits of safe apnea time.(4) This is particularly true if succinylcholine is used, as there is no reversal agent for succinylcholine-induced muscle paralysis. The time of muscle tone recovery to 50% of the baseline value after a single bolus of succinylcholine with induction dose (1 mg/kg) can reach 8.5 minutes on average.(4)

Recently, sugammadex was made available to reverse the muscle paralysis achieved with vecuronium and rocuronium.(5, 6) Complete reversal can be obtained within 2 minutes if an adequate dose of sugammadex is administered after a routine induction dose of rocuronium (0.6 mg/kg). The availability of sugammadex has the potential to change current anesthetic guidelines. However, its advantages have not been systemically assessed.

In a classic anesthetic induction, a sedative-hypnotic medication such as propofol is administered. After an IV bolus of propofol (1-2 mg/kg) is given, it reaches its peak level in the brain in about 1 minute and quickly declines.(7) For classic induction (CI), a bolus of neuromuscular blocking drug (NMBD), commonly rocuronium (0.6 mg/kg), is administered after the provider attempts mask ventilation and proves its effectiveness. However, new recommendations state that a paralytic agent should be administered if mask ventilation is proven difficult or impossible.[1] Therefore, attempted mask ventilation wastes time if a "cannot ventilate and cannot intubate" scenario is encountered. In addition, classic teaching has two more major disadvantages. First, the majority of "cannot intubate and cannot ventilate" situations are not anticipated. Second, most aspiration events that occur during induction are with mask ventilation. Therefore, the classic airway management of an unanticipated difficult airway is not optimized, particularly in terms of utilizing apnea oxygenation time.

A "time principle induction" (TPI) has been tested by an administration of a non-depolarizing neuromuscular-blocking agent before a sedative-hypnotic is given in the operating room setting.(8-13) It is also tested in an emergency room setting and has been proven that there are no differences in intubating conditions and the success rate of first attempted intubation between the two approaches, CI and TPI.(14) However, even with the

non-inferiority results of TPI vs. CI, the sample size of the previous studies were small. More importantly, the non-depolarizing paralytic agent was given 20 seconds before administering a sedative,(8) or the sedative was given at the onset of clinically observed muscle weakness.(9) (10) (11) (12) (13) Therefore, patient awareness of muscle paralysis before a loss of consciousness and post-operative recall is of great concern, although previous studies have not demonstrated whether this occurs.

The TPI can be modified – Modified Time Principle Induction (MTPI) – by administering a sedative and a neuromuscular blocking agent nearly simultaneously to minimize the likelihood of awareness of muscle paralysis before a loss of consciousness (Figure 1). In CI, a propofol bolus (1-2 mg/kg) will typically result in apnea in about 60 seconds. Attempted mask ventilation, followed by administration of NMBD, will take over 3 minutes, as it takes about 3 minutes to reach maximal muscle paralysis. If an intubation attempt is unsuccessful followed by an unsuccessful supraglottic airway (SGA) insertion, this will likely encompass an additional two minutes of time. If sugammadex (16 mg/kg) is given with return of adequate spontaneous breathing occurring 2 minutes after administration, the total apnea time will be 8 minutes. In a MTPI, patients would receive a non-depolarizing NMBD first, like rocuronium (0.6 mg/kg), immediately followed by a sedative-hypnotic, like propofol 1-2 mg/kg, without waiting for the onset of muscle weakness. Once apnea occurs, attempted intubation starts. If the intubation is not successful, it is followed by attempted mask ventilation, and then SGA ventilation (each step takes 1 minute). If none of them are successful, sugammadex is given. A total of 5 minutes of apnea time is needed to regain adequate spontaneous breathing. The apnea oxygenation time is shortened by 3 minutes or by 43%. Therefore, the need for invasive airway management will likely be reduced. Since the

sedative-hypnotic and muscle relaxant are administered simultaneously, the awareness of paralysis before loss of consciousness is unlikely to occur.

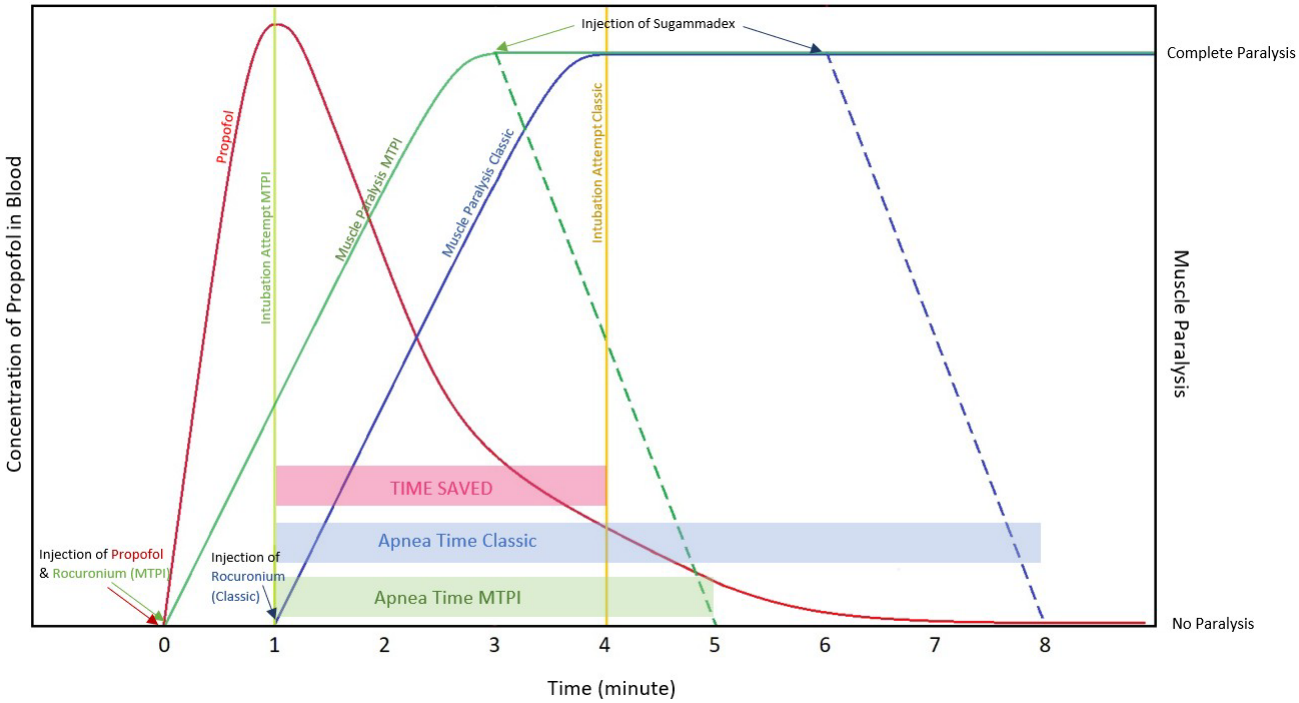

Figure 1. Schematic demonstration of intubating conditions created by Classic Induction vs. Modified Time Principle Induction (MTPI) with propofol and rocuronium. Propofol concentration in plasma in the brain (red line). Rocuronium induced muscle paralysis for classic induction (blue solid line) and Modified Time Principle Induction (green solid line). Muscle paralysis reversal after Sugammadex after MTPI (green dotted line) and classic induction (blue dotted line).

2. Hypothesis

Intubation conditions between patients receiving MTPI and CI are comparable. We will test this hypothesis by comparing time to intubation between the two techniques.

3. Specific aims

3.1 To assess and compare the conditions for tracheal intubation obtained with MTPI and that obtained with CI.

3.2. To compare the efficiency of tracheal intubation with the two induction techniques.

3.3. To determine the rate of awareness during induction and post-operative recall of muscle weakness.

4. Patient enrollment

This study will be carried out in the main operating rooms at Memorial Hermann Hospital in the Texas Medical Center (TMC). The study team will approach the patients in the respective preoperative holding area after reviewing their medical records to determine eligibility. Once the study team believes that a particular patient is eligible to participate in the study, the study team will provide that patient with detailed information about the study and obtain informed consent from the patient.

4.1. Inclusion criteria:

I. 18 or older years of age

II. BMI >30 kg/M^2 or Mallampati class III or IV

III. Requiring general anesthesia and endotracheal intubation

4.2. Exclusion criteria:

I. Acute and chronic respiratory disorders, including COPD and asthma

II. ASA physical status classification > III

III. Emergency surgery

IV. Induction requiring cricoid pressure

V. Patients requiring awake intubation

VI. Pregnant women

VII. Patients who require an induction dose of propofol less than 1 mg/kg

VIII. Untreated ischemic heart disease

IX. Contraindication to mask ventilation

X. Allergy to propofol, rocuronium, or Sugammadex

XI. Induction requiring succinylcholine

Randomization and Blinding

Patients will be randomly assigned to the MTPI group and the Classic Induction group (control) using an online randomization program (https://www.randomizer.org/#randomize). A concealed envelope will be opened prior to induction. A study arm specific handout of induction instructions will be handed to the anesthesia provider. Laryngoscopy will be done with C-MAC and the entire laryngoscopy and entire intubation procedure will be recorded and saved. Study team members converting the video recorded data to digital data will be blind to the interventions. Once the study is completed and the digital data is collected, the study team members will be unblinded.

5. Outcomes

5.1 Primary outcome: The time between laryngoscope insertion into mouth and the onset of ventilation after tracheal intubation with MTPI vs. CI as visualized with C-MAC

5.2 Secondary outcomes:

5.2.1 The success rate of first attempted tracheal intubation, number of attempts, and failed intubation.

5.2.2 The best glottic view

5.2.3 Provider determination of intubating conditions, based on whether intubation was classified as “Not difficult” or “Difficult”

5.2.4 Vital signs during intubation including HR, BP, end-tidal CO_2, and SpO_2

5.2.5 Injury associated with intubation, including injury of teeth, lips, tongue, and pharyngeal bleed

5.2.6 Patients’ physical response during intubation, including moving and coughing

5.2.7 Post-operative survey in PACU and post-operative day #1 to assess awareness of muscle paralysis before loss of consciousness, sore throat, nausea, and vomiting, and overall satisfaction. Please refer to the post-operative survey form.

5.2.8 Recollection of pain on induction.

6. Study protocol

After providing informed consent, the subjects will receive premedication in the usual manner. Premedication typically includes 0-2 mg of IV midazolam at the discretion of the care team. Subjects will then be transported to the operating room and placed on the operating room table in the supine position with the head in the neutral position on a pillow. Operators who will perform endotracheal intubation are limited to an anesthesiology attending, anesthesiology residents who have performed greater than 75 endotracheal intubations, a CRNA or Anesthesia Assistant with working experience greater than 1 year.

Mask ventilation or supraglottic ventilation will be utilized if the first intubation attempt is not successful.

Standard monitors for general anesthesia will be applied, including ECG, blood pressure, pulse oximetry, and capnography. Pre-oxygenation via a plastic mask will be carried out with a flow rate of 10-liter min−1 of 100% O_2 until the expired O_2 concentration reaches ≥80%. Randomization with random allocation of patients to a group and concealment of treatment from the patient and intubation scorer is carried out once informed consent is signed. Patients from both study groups will receive 1 mg/kg of lidocaine intravenously, followed by an opioid such as fentanyl (1-2 mcg/kg), prior to administration of induction drugs. Patients assigned to MTPI will then be given rocuronium (0.6mg/kg), followed by propofol intravenously as a single bolus within 10 seconds. A typical propofol bolus for induction ranges from 1-2mg/kg, depending on the patient's age, medical history, and co-morbidities. Propofol dosing will be at the discretion of the care team. Patients will count down from one hundred. Once apnea occurs, as indicated by a lack of respiratory effort, the eyes will be taped, and intubation with C-MAC (Karl Storz 8403ZX, Tuttlingen, Germany) is initiated. An additional attempt of intubation is defined as the re-insertion of the C-MAC or insertion of another type of laryngoscope. The documentation of the intubation is performed by the study team. The laryngoscopy is continuously recorded and saved. The study team member who views the video of intubation and scores the difficulty of intubation and the glottic view is blind to the interventions. Patients assigned to CI will be induced as per routine care using lidocaine 1 mg/kg, an opioid such a fentanyl (1-2 mcg/kg), propofol 1-2 mg/kg, and rocuronium 0.6 mg/kg, and the intubation will be performed with a C-MAC. Patients will also count down from one hundred. The medications used for induction of anesthesia in both

arms of the study are those used for routine anesthesia care. In both study arms, dosing of medications for induction of anesthesia is standardized (lidocaine 1 mg/kg, fentanyl 1-2 mcg/kg, propofol 1-2 mg/kg, and rocuronium 0.6 mg/kg). The only difference between the two arms will be the timing of the medication administration, and the order in which medications are administered. The documentation of induction and intubation will be the same as that of the MTPI group. Vital signs and other parameters will continuously be recorded in the intraoperative record. Emergence and extubation are not protocolized. Once the patient arrives in the PACU, the study team will assess the patient 30 min after arrival and attempt to conduct a post-operative survey (see PACU Patient Survey).

7. Data acquisition and analysis

All ventilatory settings and measured parameters displayed on the operating room ventilator (Datex Ohmeda AS/5, Helsinki, Finland), including expired tidal volume, flow waveforms, end-tidal carbon dioxide partial pressure, exhaled carbon dioxide waveforms, and vital signs displayed on the monitor will be recorded intra-operatively in the electronic medical record and video recorded from the time of pre-oxygenation and 5 minutes after intubation. Specific time points that will be collected are induction time, onset of apnea, beginning of intubation attempt, and time to successful intubation (identified by time between laryngoscope insertion into the mouth and the onset of ventilations after tracheal intubations with MTPI vs. CI with C-MAC).

8. Predicted outcome and its significance

The study team assumes that MTPI will be non-inferior to CI in the rate of 1st attempt tracheal intubation success. Additionally, we predict no significant difference in intubation time, glottic view, rate of successful intubation, rate/severity of injury associated with tracheal intubation, and the rates of awareness of muscle paralysis before loss of consciousness using the two different types of approaches. The study team predicts that MTPI will create similar intubating conditions compared to CI and will shorten the apnea time by 3 minutes (a reduction in apnea time by 37.5%) if a "cannot intubate and cannot ventilate" scenario is encountered and sugammadex rescue is used to reverse muscle paralysis. By shortening apnea time, we expect that MTPI would improve difficult airway management and therefore patient outcomes.

Positive outcomes expected from this study include increased efficiency in induction and intubation. Another benefit would be no longer needing to mask ventilate. Since 60% of aspiration occurs during mask ventilation, avoiding mask ventilation will significantly reduce aspiration rates. Also, a high dose (1.2 mg/kg) of rocuronium recommended for rapid sequence induction may not be needed. Furthermore, it is known that succinylcholine is associated with increased muscle aches, cardiac arrest, and mortality rates. The new method of modified time principle induction being done in this study may lead to a decreased need for succinylcholine as an option for muscle paralysis.

9. Sample Size Calculation

The primary outcome is time between laryngoscope insertion into mouth and the onset of ventilation after tracheal intubation in CI vs. MTPI as visualized with C-MAC. Among successful intubations, laryngoscopy time with a C-MAC averaged 46 seconds (95% CI, 40-

51).[15] We assume the time required for tracheal intubation with the two induction approaches using a C-MAC is not significant if the time between the two approaches is smaller than 15 seconds. With 80% power at 0.05 significance, a total sample size is 130 patients, with 65 patients in each arm. To account for a drop rate of 15%, we will enroll a total of 154 patients.

10. Risk Assessment

10.1. Potential complications associated with induction and intubation are expected to be the same between the two groups. In another words, this study would be unlikely to add risk or reduce the existing potential risk of induction and intubation.

10.2. Adverse effects of medications: Propofol and fentanyl are routinely used for anesthesia care. We will exclude the patients who are allergic to these two medications. Midazolam is routinely used as pre-medication. Any risk associated with these three medications will not be altered due to the study. All other medications will not be restricted to use for patient care including antiemetics.

10.3. Patient awareness of muscle weakness before a loss of consciousness is a potential risk of the study. However, previous studies using a time principle induction have not demonstrated this in both the operating room and emergency room settings. Therefore, we do not anticipate any increased risks of awareness of muscle weakness in the study group when compared to the control group.

11. Data Safety Monitoring

11.1. A data safety monitor will review the trial protocol and the accumulated data on an ongoing basis for the duration of the trial. This individual will be monitoring the

benefits and risks to the participants of the trial in order to protect patient safety, credibility of the trial and validity of the study results.

11.2. The data safety monitor will be unaffiliated with the study and will have no financial, scientific, or other conflict of interest with the trial. The data safety monitor will have experience in the proper conduct of clinical trials and statistical knowledge in order to evaluate the results of the data.

11.3. The data safety monitor will perform data reviews at 30, 60, 90, 120, and 143 patients, or sooner if indicated.

11.4. Specific roles of the data safety monitor include oversight and analysis of study data to ensure continuing safety of trial participants, efficacy of the study intervention, and data integrity. By reviewing the data as it accumulates, the data monitor can identify significant trends or issues, and provide recommendations for changes in the study as needed.

12. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or others

The study team does not anticipate increased risk of intraoperative events or other complications associated with this study as compared with routine care. Any adverse events and complications occurring in either group will be reported in the Data Collection Sheet.

12.1. Adverse events (AE) will be obtained and documented by the investigators performing data collection and by questioning or examining the patient. All new complaints and symptoms (i.e., those not existing before the signing of informed consent) will be recorded on the AE CRF.

12.2. AE's will be characterized in terms of their start and stop dates, start and stop times, intensity, action taken, relationship to research study, subject outcome, and whether the AE led to an SAE.

12.3. The study team will perform a review of adverse events after enrollment of 20 subjects.

13. Privacy/Confidentiality Issues

Measures will be taken to prevent lapses in confidentiality from occurring. Only key study personnel will have access to identified information. Exported and extrapolated data will be stored on a password protected UTHealth computer that only key study personnel can access. Any paper records will be kept in a drawer with a lock within Dr. Jiang's office.

14. Follow-up and Record Retention

Records will be kept through the HIPAA-compliant servers of McGovern Medical School. All the documents will be kept in Dr. Markham's office in the drawer with a lock. All research tests will be performed under a code that protects the identity of the participants. Records of experimental procedures will be kept at least 6 years following the publication of the study results. At that time, research data will be destroyed.

15. Milestone of the study

- August 15, 2022. Approval of IRB application
- August 16, 2022. Initiation of the study
- August 29, 2022. Completion of the study – the first 10 patients

- November 21, 2022. Completion of the study – first 100 patients
- January 16, 2025. Completion of the study total 154 patients

16. Cost and resources

All the equipment needed for the study is for routine anesthesia care and is available in the operating room. Participation in this study will not cost more than that of ordinary care. Since this study imposes minimal risk, and little effort on the participants is needed, the participants will not be compensated and will be discussed at the time when consent is obtained. Dr. Markham will provide an encrypted laptop computer for the study team.

17. References

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18. Appendix

1: Grading System for Studied Intubation Methods

Score	Modified Time Principle Induction (MPTI) (n=)	Classic Induction (CI) (n=)
3		
2		
1		
0		

Induction condition scores: 3 (Excellent) – Jaw is fully relaxed, muscles completely paralyzed, and vocal cords are abducted. 2 (Good) – Similar to score 3 but with mild movement and coughing. 1 (Poor) – Strained or firm jaw; bucking action; and moving vocal cords. 0 (Failure to intubate).

2: Patient Post-Operative Survey

Patient
Name: _____ MRN: _____ DOB: ____/____/____

Post Anesthesia Care Unit Survey of Modified Time Principle Induction
Intubation conditions achieved with rapid co-administration of Rocuronium and Propofol versus classical induction: A Prospective Randomized and Blind Trial.

Describe the last thing you remember before falling asleep.

_____

_____

_____

What is the last number you remember counting down from 100 before falling asleep during anesthesia?

_____

Did you feel awake during the surgery? YES NO

Did you feel like you could NOT move during the surgery? YES NO

If yes, did you feel scared? YES NO

Did you feel like you could NOT breathe during the surgery? YES NO

If yes, was it happening when you were waking up? YES NO

(Continue to next page)

Using the classification scale below, please indicate what classification you fall under regarding your level of awareness during anesthesia care.

Table 1. Michigan Awareness Classification Instrument

Class 0: No awareness
Class 1: Isolated auditory perceptions
Class 2: Tactile perceptions (*e.g.*, surgical manipulation or endotracheal tube)
Class 3: Pain
Class 4: Paralysis (*e.g.*, feeling one cannot move, speak, or breathe)
Class 5: Paralysis and pain
An additional designation of "D" for distress is included for patient reports of fear, anxiety, suffocation, sense of doom, sense of impending death, *etc.*

CLASS NUMBER: _____

On a scale of 0-10, how would you rank you level of throat soreness?
Zero being no sore throat at all and ten being the worst sore throat you have ever felt (zero is no pain and 10 means the worst pain).

0 1 2 3 4 5 6 7 8 9 10

Did you feel nausea? YES NO

Did you vomit after the surgery? YES NO

On a scale of 0-10, what is your level of satisfaction with your anesthesia experience?
Zero being not satisfied at all and ten being extremely satisfied.

0 1 2 3 4 5 6 7 8 9 10

Signature: _____ **Date:** _____

Patient Post-Operative Survey: Patients will fill out the survey in the PACU based on their experience. They will also document the last number they remember counting while in the operating room. The provider will later compare the number stated in the operating room (recorded separately) to the number the patient remembered in the PACU.